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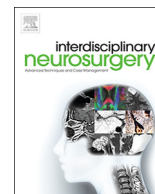
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Technical Notes & Surgical Techniques

Pineoblastomas: A long-term follow up study of three cases in Helsinki Neurosurgery



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ABSTRACT

Background: Pineoblastomas are very rare malignant lesions with a bad prognosis and high mortality during the first five years from diagnosis.

Report of cases: We present a retrospective review of three patients with histologically confirmed pineoblastomas consecutively operated on between 1997 and 2015. One of our patients died > 14 years after surgery, and the other 2 patients are still alive and in good condition without recurrence of the disease > 12 years after surgery. All of them underwent gross total resection and craniospinal radiotherapy. Individualized scheme of chemotherapy was administered in two cases. The cornerstones for the surgical resection of pineoblastomas are reported.

Conclusions: A proper multidisciplinary management of pineoblastomas, which associates gross total microsurgical resection of the lesion and an adjuvant therapy determined by our neurooncology team based on accurate craniospinal adjuvant radiotherapy with boost of radiation on the tumoral bed, and when needed, an adequate but aggressive medulloblastoma-like chemotherapy, may improve the overall survival of these malignant lesions.

1. Introduction

Pineoblastomas are very rare malignant lesions with a bad prognosis and high mortality during the first five years from diagnosis [1,2].

Pineal region tumors represent < 1% of all intracranial neoplasms. PPTs, a group of relatively heterogeneous pineal lesions, comprise around 14–27% of all pineal region tumors [1]. In 2007, the World Health Organization (WHO) Classification of Central Nervous System Tumors recognized 3 different PPTs: the WHO grade I pineocytoma (14–30%), the WHO grade II-III PPT with intermediate differentiation (20–62%), and the WHO grade IV pineoblastoma (24–50%). This wide variation in the relative incidence in the published series reflects the overall rarity of these tumors, and the variability in the used grading and terminology [1,3]. The 2016 WHO Classification of Central

Nervous System Tumors did not add any new feature to the previous classification [4].

In this paper we describe our multidisciplinary management (gross total resection -GTR-, radiotherapy and chemotherapy) of three pineoblastomas operated consecutively in Helsinki between 1997 and 2015.

2. Report of cases

Twenty-three PPTs were operated in Helsinki Neurosurgery during the study period. Three histologically confirmed WHO grade IV pineoblastomas were found. Our neuropathologist (OT) re-evaluated the histological samples and reconfirmed the diagnosis in two of them (case 2 and case 3) (Fig. 1). Patient's information was revised in the Finnish population register in December 2018 to determine their current status.

Abbreviations: CCNU, lomustine; GTR, gross total resection; PPT, pineal parenchymal tumor; VCR, vincristine; WHO, World Health Organization

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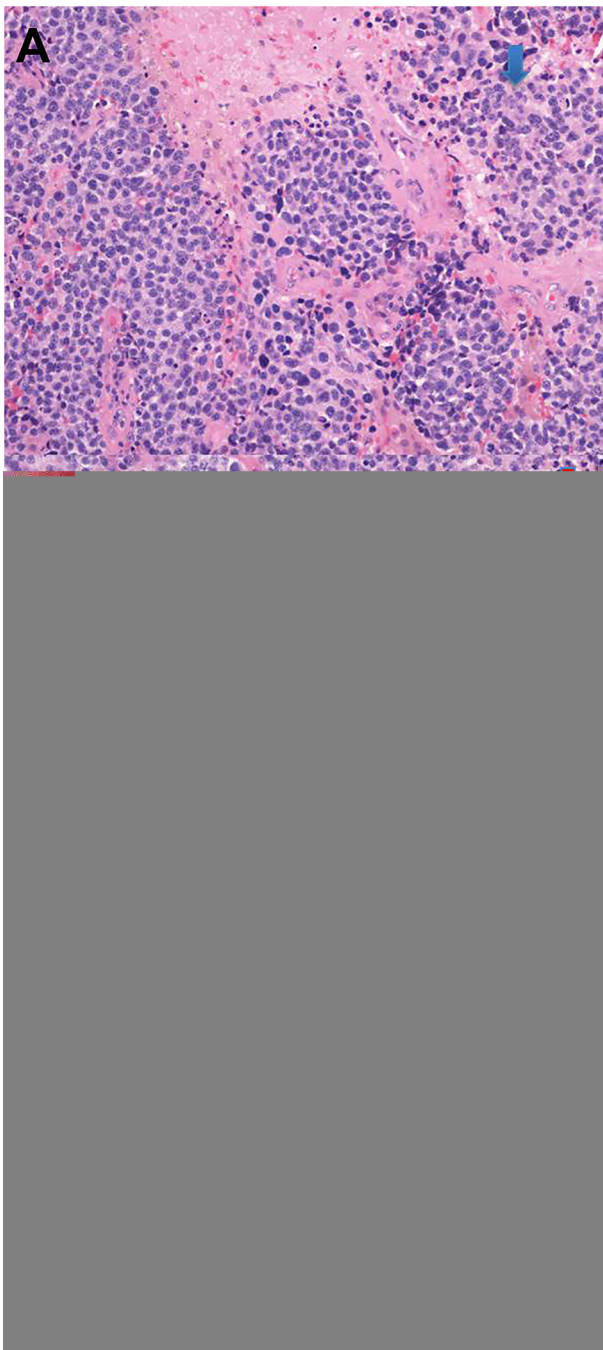


Fig. 1. Microphotographs of a surgically treated pineoblastoma (Case 3). A, B. Hematoxylin and eosin stain with high cellularity, numerous mitotic figures, (38 mitosis/10 High Power Fields) and necrosis. Homer Wright and Flexner-Wintersteiner rosettes (red arrow) and fleurettes (blue arrow) are also seen C. Ki67 index of 60%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In Helsinki Neurosurgery as previously described, almost all pineal tumors are approached by a supracerebellar infratentorial route or by an occipital interhemispheric access with the patient in the sitting praying position [5,6].

Exceptionally, other approaches such as the subtemporal approach, telovelar approach to the fourth ventricle, or even the anterior interhemispheric approach might be used.

Acute and rapidly progressive concomitant hydrocephalus requires external ventriculostomy, endoscopic third ventriculostomy, ventriculoperitoneal/ventriculoatrial shunt, or direct removal of the pineal

Table 1

Microsurgical pearls in the microsurgical management of pineoblastomas.

1. The proper analysis of the preoperative imaging associated to the experience of the surgeon determines the optimal approach for pineoblastomas. Whether the tumor consists of a large supratentorial segment extending behind and above the corpus callosum and the deep venous system, an occipital interhemispheric route remains as our best approach. In contrast, an infratentorial lesion behind and below the neurovascular structures of the pineal region generates an optimal location for the supracerebellar infratentorial approach. Giant lesions might require a combined use of both approaches in single or different stages.
2. Different to other malignant tumors such as infiltrative gliomas, the preoperative evaluation of the MRI imaging and the intraoperative observation of malignant pineoblastomas determine that this aggressive lesion preserve some grade of differentiation from the surrounding structures without aggressive microscopic infiltration. This feature may allow a complete surgical resection without damage of the neurovascular structures. (Fig. 3)
3. A critical stage during the microneurosurgery is closely related with the adherence of the tumor and the infiltration of external layers of the deep venous structures, particularly the internal cerebral veins. The tumor should be carefully dissected by water dissection technique, cotton dissection, and using microscissors and bipolar microforceps. Along our experience, we highly suspect that most of the residual tumors are those attached to these vessels. (Figs. 2 and 3)
4. When a high-vascularized area is suspected, intraoperative indocyanine green angiography is used to define vascular structures.
5. Along the microsurgical removal, an internal decompression with a thumb regulated suction tube and bipolar or ring microforceps is performed aiming to find and open the posterior wall of the third ventricle.
6. Once medial, lateral, and superior surfaces of the tumor are separated from the adjacent tissue, under soft but continuous traction –using bipolar microforceps or ring microforceps– the tumor is separated from its inferior border by using a thumb regulated aspiration. A continuous irrigation maintains a clean surgical field.
7. A microsurgical mirror or an endoscope may be helpful to recognize some residual tumor, particularly at the inferior border of the field.
8. A careful hemostasis with bipolar coagulation, Surgicel® (Ethicon Inc., Johnsons & Johnson: Switzerland) and Tachosil® (Takeda Austria GmbH: Linz, Austria) is carried out, and the closure is accomplished under the microscope.

lesion according to the emergency, cytology study of the cerebrospinal fluid, presence of tumor markers in blood or spinal fluid, and preference of the surgeon. However, slow progressive hydrocephalus is generally treated by direct removal of the lesion.

Careful microneurosurgery aiming a gross total resection of the tumor is performed following some principles developed in our department (Table 1) [7,8]. When the histological diagnosis is confirmed, the neurooncology team composed by a neurosurgeon, an oncologist, a neuropathologist, a radiologist, and a neurologist determine all further management and complementary treatment. In case of pineal tumors, we must remark the importance to determine the treatment modality for these rare and complex lesions, based on the oncological advisory commission of every neurooncological department.

2.1. Case 1

An eighteen year-old female was referred from the neurological department in April 2001. Three months prior, she presented occasional double vision associated with vertigo, vomiting and early morning headache. The visual accuracy diminished gradually on the left eye. CT and brain MR revealed a $3.2 \times 2.4 \times 1.8$ cm homogeneously enhancing pineal region lesion with a cystic component associated with hydrocephalus (Fig. 2).

A ventriculoperitoneal shunt was initially placed after negative cerebrospinal fluid cytology study and absence of tumor markers in blood and spinal fluid. After few days, the patient underwent a supracerebellar infratentorial approach in sitting position with removal of the tumor in April 2001. During the postoperative course, MRI images showed still some contrast enhancement at the level of the cerebral internal veins with high suspicion of residual tumor. In the following MRI studies after adjuvant therapy, this contrast enhancement disappeared and no evidence of residual tumor was observed since August 2001 (Fig. 2).

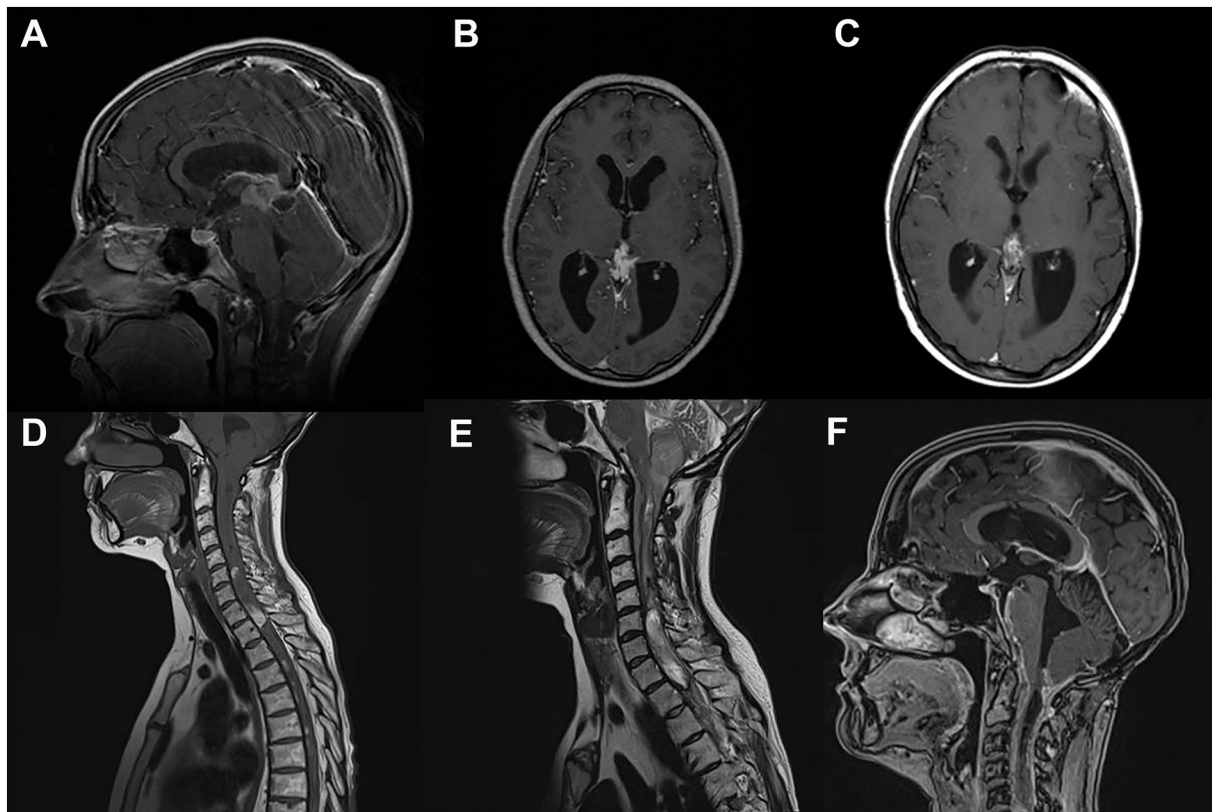


Fig. 2. Pre-operative image of a WHO grade IV pineoblastoma (A). B. Post-operative cranial MRI (July 2001) showing some contrast enhancement at the level of the internal cerebral veins, which disappeared in the following MRI study (C, August 2001). D–F Last craniospinal MRI (July 2015) revealing tumoral infiltration of the midbrain and spinal cord without pineal recurrence.

The histologic diagnosis was grade IV pineoblastoma. The spinal MRI studies did not determine spinal metastasis, and the patient initiated fractionated craniospinal radiotherapy three weeks after the surgery based on the high possibility of subtotal resection of the tumor, and on the relative young age of the patient. However, this treatment had to be suspended after 2 weeks due to meningitis and the shunt was removed to start systemic antibiotic therapy. Finally, a protocol of 36 Gy craniospinal radiation with an additional 25 Gy boost of radiation on the tumoral bed, divided in a daily dose of 1.8 Gy, finished on August 3, 2001. Concomitant chemotherapy was not administered due to the history of infection. However, post radiotherapy adjuvant chemotherapy was based on lomustine (CCNU) and vincristine (VCR) protocol.

One year after surgery, the patient who clinically presented slowly progressive hydrocephalus required a definitive ventriculoperitoneal shunt, which was revised once more after few weeks.

A two years follow-up brain MRI demonstrated absence of tumor recurrence. However, the spinal MRI demonstrated a cervicothoracic syringomyelia and probable arachnoiditis. The patient had walking difficulties and underwent rehabilitation and equine-assisted therapy. Seven years after surgery, the patient had still walking difficulties at the clinical evaluation.

Nine years after surgery, no residual tumor was found at craniospinal MRI studies. Syringomyelia was stable and smaller compared to the previous MRI. The patient was paraparetic, but was still able to walk.

In January 2015, fourteen years after surgery, the patient presented a right side VI cranial nerve paresis and slight facial paresis. The craniospinal MRI revealed important tumoral infiltration of the midbrain and spinal cord. Nonetheless, no recurrence in the pineal region was observed in July 2015 (Fig. 2). The patient died from pneumonia in September 2015, 173 months after surgery.

2.2. Case 2

A three year-old female was referred from the pediatric department in November 2004. A month prior, she presented some eye movement problems, vomiting, and balance difficulties. Brain MRI revealed a $2.7 \times 3.1 \times 2.7$ cm homogeneously enhancing pineal region lesion with a cystic component associated to hydrocephalus (Fig. 3).

A ventriculoperitoneal shunt was initially placed after negative cerebrospinal fluid cytology study and absence of tumor markers in blood and spinal fluid. Few days later, the patient underwent a supracerebellar infratentorial approach in sitting position with GTR of the tumor in December 2004. The postoperative course was uneventful.

The histologic diagnosis was grade IV pineoblastoma. The histologic study determined six mitoses for 10 High Power Fields, and a Ki-67 labeling index of 70%. Necrotic foci were also seen in the samples.

Six weeks after the surgery, the pediatric patient received adjuvant chemotherapy and fractionated craniospinal radiotherapy based on an aggressive medulloblastoma protocol. 36 Gy craniospinal radiation with an additional 18 Gy boost of radiation on the tumoral bed was divided in a daily dose of 1.8 Gy. Concurrently, VCR 1.5 mg/m^2 once a week for 6 weeks was set. Six weeks after this initial treatment, a new scheme of chemotherapy was administrated every 6 weeks with 8 cycles of CCNN: $75 \text{ mg/m}^2 \times 1$; cisplatin: $75 \text{ mg/m}^2 \times 1$; and VCR: $1.5 \text{ mg/m}^2 \times 3$ on days 0, 7, and 14.

The last evaluation of the patient was performed in May 2018, and she did not show any neurological deficit. Brain MRI did not show any recurrence as well. The patient continues to do well > 170 months following surgery.

2.3. Case 3

A twenty five year-old female was referred to our department with

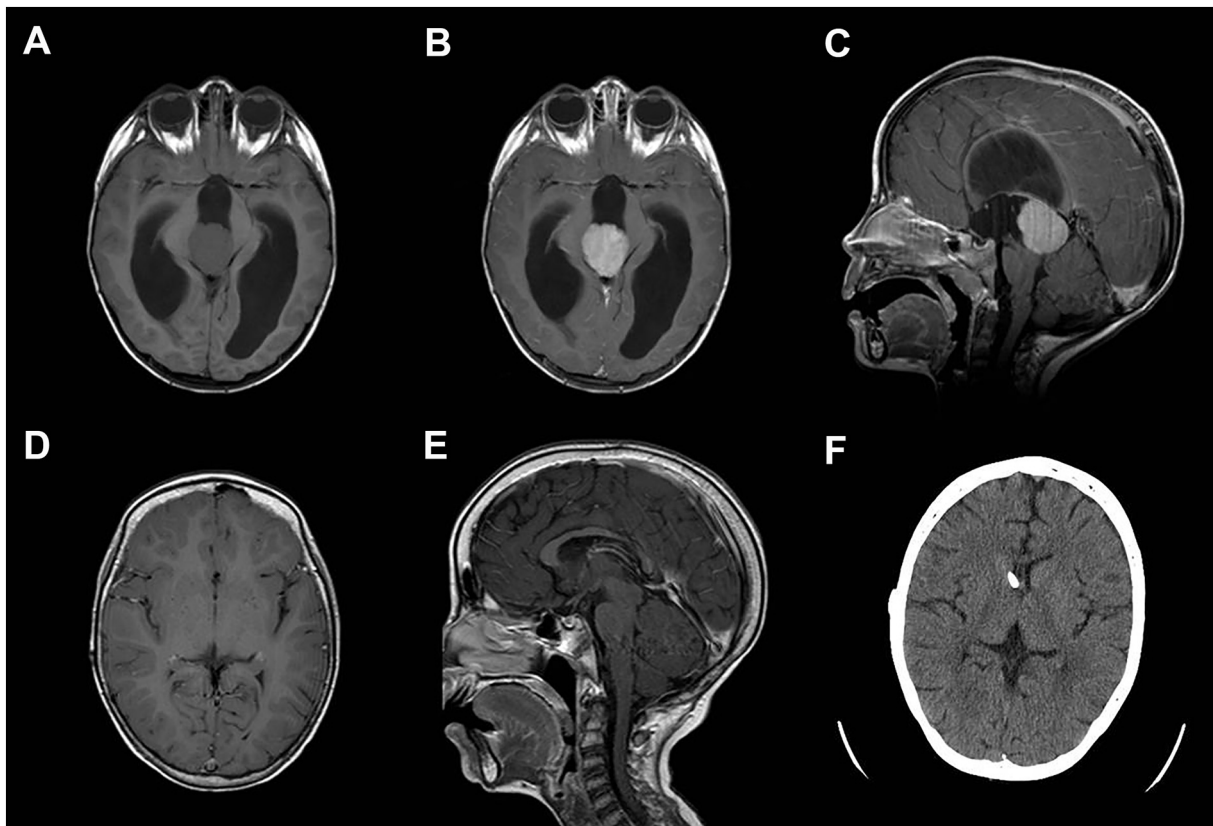


Fig. 3. Pre- (A–C) and post-operative (D, E) MRI images of a WHO grade IV pineoblastoma. F, Last cranial computed tomography study (May 2018).

deterioration of consciousness and acute hydrocephalus associated with a pineal region lesion.

The patient underwent immediately a supracerebellar infratentorial approach in sitting position with GTR of the tumor in April 2006. During the postoperative course, the patient improved partially her consciousness state and developed a Parinaud's syndrome. A cranial CT showed the persistence of hydrocephalus, and an endoscopic third ventriculostomy was carried out. However, the procedure was insufficient and finally a ventriculoperitoneal shunt was placed.

The histologic diagnosis was grade IV pineoblastoma. The histologic study determined 38 mitoses for 10 High Power Fields, and a Ki-67 labeling index of 60%. Necrotic foci were also seen in the samples, but no tumoral activity was found in the cerebrospinal fluid. Six weeks after the surgery, the patient received adjuvant fractionated craniospinal radiotherapy. 36 Gy craniospinal radiation with an additional 18 Gy boost of radiation on the tumoral bed was divided in a daily dose of 1.8 Gy. The neurooncology team did not recommend the administration of adjuvant chemotherapy based on the age, absence of extra-pineal tumor activity and gross total resection of the tumor.

The gaze paralysis improved gradually with very occasional double vision at the last follow-up in October 2017. Brain MRI did not show any recurrence as well. The patient continues to do well > 152 months following surgery.

3. Discussion

In this paper we describe our multidisciplinary management (GTR, radiotherapy and chemotherapy) of three pineoblastomas operated in Helsinki between 1997 and 2015. One of our patients died > 14 years after surgery, and the other 2 patients are still alive and in good condition without recurrence of the disease > 12 years after surgery. All of them underwent GTR and craniospinal radiotherapy with boost of radiation on the tumoral bed. Individualized scheme of chemotherapy

was administered in two cases.

3.1. Outcome in pineoblastoma patients

Several studies have reported about the poor outcome of pineoblastomas. A median survival of 20 months and a 5-year survival rate of 10% were initially reported [9–11]. In 2007, Nakazato et al. [1] summarized that median postsurgical survivals of pineoblastomas vary between 24 and 30 months, and the main causes of death are represented by metastases within the central nervous system. The authors mentioned that the prognosis is affected by the extent of the disease at the time of diagnosis, which is determined by cerebrospinal fluid and spine MRI examination, as well as by the extent of resection and radiotherapy. However, the outcome seems to be better when the tumor is discovered incidentally.

A literature review conducted by Tate et al. [2] in 2012 about the long-term postsurgical prognosis of patients with pineoblastomas concluded that they have an overall survival rate of 54% (175 of 299 patients) at a mean follow-up of 31 ± 1.9 months (range, 1–159 months). The analyses demonstrated a markedly worse prognosis for children aged ≤ 5 years. The prognosis was inversely proportional to the degree of resection. Thus, the five-year survival rate was 84% for GTR, 53% for subtotal resection, and 29% for debulking. Multivariate analysis indicated that not achieving GTR markedly worsened patient survival, independently of variables as very young age, intracranial dissemination, and other combinations of adjuvant therapies. They pointed out that pediatric and adult pineoblastomas have a different behavior and should be separately considered when analyzing their response to surgical and adjuvant therapy.

Considering pineoblastomas in children, Parikh et al. [12] recently reported their experience in 41 pediatric and adult pineoblastoma patients with a median age at diagnosis of 5.5 years (0.4–28.1) and a median follow-up of 34.5 months (4.7–183.5). All patients except 3

were younger than 20 years old. Nineteen patients, (17 younger than 5 years old) experienced tumor relapse with a median progression-free survival of 11.3 months, and 18 ultimately succumbed to their disease. Patients who died or experienced treatment failure were younger (median, 2.69 vs 6.5 years), and had a metastatic disease at diagnosis in most of the cases. When analyzing only patients 5 years of age or older with focal disease at presentation, those who had a GTR or near-total resection had greater overall survival compared to patients who underwent subtotal resection or biopsy (75.18 versus 48.57 months), and no patient died for tumor progression. They concluded that young age, metastatic disease at presentation, and tumor relapse are associated with a poor prognosis. Therefore, maximal tumor resection should be the goal in patients older than 5 years with focal disease.

Regarding radiosurgery as main therapy for pineoblastomas, a study based on the stereotactic Gamma Knife radiosurgery of histologically defined tumors, reported an actuarial local control and a survival rate of 27% and 48% at a 5 years follow up, respectively. In this study, the authors analyzed 13 patients who underwent a subtotal resection in 7 cases, a biopsy in 5, and a GTR in only one case [13]. These results contrast with the 80% survival rate and 80% actuarial local control reported at a 20 years follow up for germinomas, which are the most radiosensitive tumors of the pineal region [13,14].

3.2. Factors associated with better outcome in our series

The general prognosis of pineoblastomas is considered poor and as mentioned, factors such as minor extent of the disease at the time of diagnosis, major extent of resection, radiotherapy delivery, tumors found incidentally, and adult pineoblastomas, are associated with better outcome. In children, young ages, major extent of the disease at presentation, and tumor relapse are associated with a poor prognosis.

Most of the authors reported a low rate of GTR, with a difficult tumor control, frequent recurrences, and a high mortality during the first five years from diagnosis [1,2,9–12]. Those findings contrast with our results, which based on the neurooncology team recommendations are the following: a) the GTR of the tumor, which we believe is the most important element aiming to obtain good long-term results, b) adjuvant craniospinal radiotherapy with boost of radiation on the tumoral bed and c) individualized aggressive medulloblastoma-like chemotherapy in children and patients with high risk of metastasis [5–8]. Some of our microsurgical pearls to achieve GTR without or with minimal complications are detailed in Table 1.

GTR might be achieved thanks to the combination of variables such as an essential proper team work (Neurosurgeon, anesthesiologist, scrub nurse and all involved personnel), adequate principles of positioning and approach, skillful microneurosurgery based on the principle “simple, clean and safe”, and not less importantly, the surgical experience of the Neurosurgeon.

Regarding the case number one, the definitive diagnosis of the last lesion as reason of death remains obscure since no autopsy has been performed. A secondary malignant tumor after radiation therapy might be also suggested. However, the retrospective analysis of the case suggests that the postoperative contrast enhancement close to the internal cerebral veins represented a small residual tumor, which due to the difficulties delivering radiochemotherapy, developed some microscopic seeding in the midbrain and spinal cord with evident further metastasis after many years.

The small number of patients represents a limitation of our study. Nevertheless, as these tumors are extremely rare, we consider especially

important to report our long-term findings in a non-selected series of patients.

4. Conclusion

A proper multidisciplinary management of pineoblastomas, based on the GTR of the lesion, accurate craniospinal adjuvant radiotherapy, and, when needed, an adequate chemotherapy, may improve the overall survival of these malignant lesions.

Disclosure

Prof. Juha Hernesniemi is an Aesculap counselor. The C. Ehrnrooth Foundation partially supports the present paper, which is part of the “Pineal region surgery” project. The authors have no personal financial or institutional interest in any of the drugs, materials, and devices described in this article.

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